rPA Vaccine Development and the "Animal Rule"

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Objectives

Regarding the Animal Rule, this presentation will show:

- Integration of the Animal Rule, the April 2002 rPA Animal Models workshop and ongoing studies
- Implementation of the Animal Rule
- Complex endeavor

Factors impacting rPA product development planning

- Contractor down-select not made when originally intended: Avecia and VaxGen
- Government-sponsored aerosol challenge animal studies
- 2 Indications: GUP (pre) and PEP (post) exposure prophylaxis
- Increasing importance of IDIQ and BioD Repository Contracts
- Bioshield: FDA/EUA, funding for increased SNS requirement
- Timeline
- Flexibility and focus is required

"Animal Rule" 21 CFR 601.91(a)(1-4) (April 1, 2004)

- Sec 601.91: Approval based on evidence of effectiveness from studies in animals.
  - (a) FDA may grant marketing approval….based on adequate and well-controlled animal studies when….product is reasonably likely to produce clinical benefit in humans.
    - (1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention
    - (2) The effect is demonstrated in more than one animal species with response expected to be predictive for humans OR a single animal model that is sufficiently well-characterized
    - (3)The animal study endpoint is clearly related to the desired benefit in humans, generally survival enhancement or prevention of major morbidity
    - (4) The kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

"Animal Rule" 21 CFR 601.91(a)(1)

- (1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention

Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity Workshop, 4-23-2002

Rhesus versus rabbit histopathology following inhalational anthrax

- Principal lesions
  - Basic changes: hemorrhage, edema, necrosis, variable leukocytic infiltrate, septicemic disease
  - Target tissue: lymphatic organs, lung, GI, and CNS
  - Pulmonary lesions typically edema and hemorrhage; pneumonia unusual
- In rhesus
  - More intense inflammation than in rabbit, particularly in CNS
  - Increased survival time compared to rabbit
- In rabbit
  - Rapid time course, fulminant septicemic disease
  - Minimal inflammation
  - Decreased CNS involvement, hemorrhage with little inflammation

Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity Workshop, 4-23-2002

- Mechanism of PA-induced protection (proposed at time of workshop)
  - Toxin neutralization antibody (anti PA)
  - Antibody to inhibit spore germination
  - Stimulation of spore phagocytosis

Bacillus anthracis

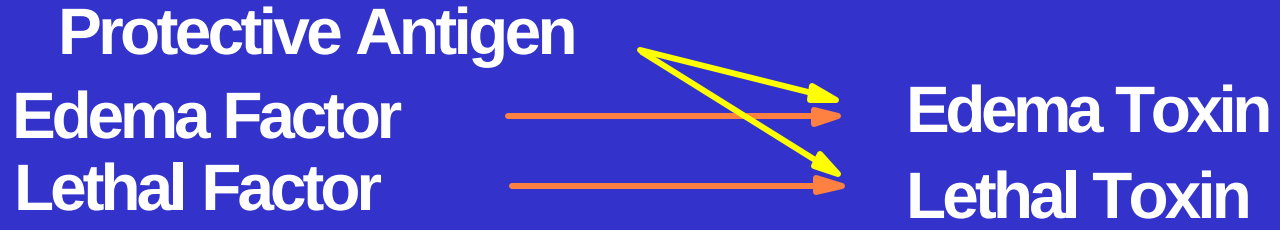
Gram-positive spore former

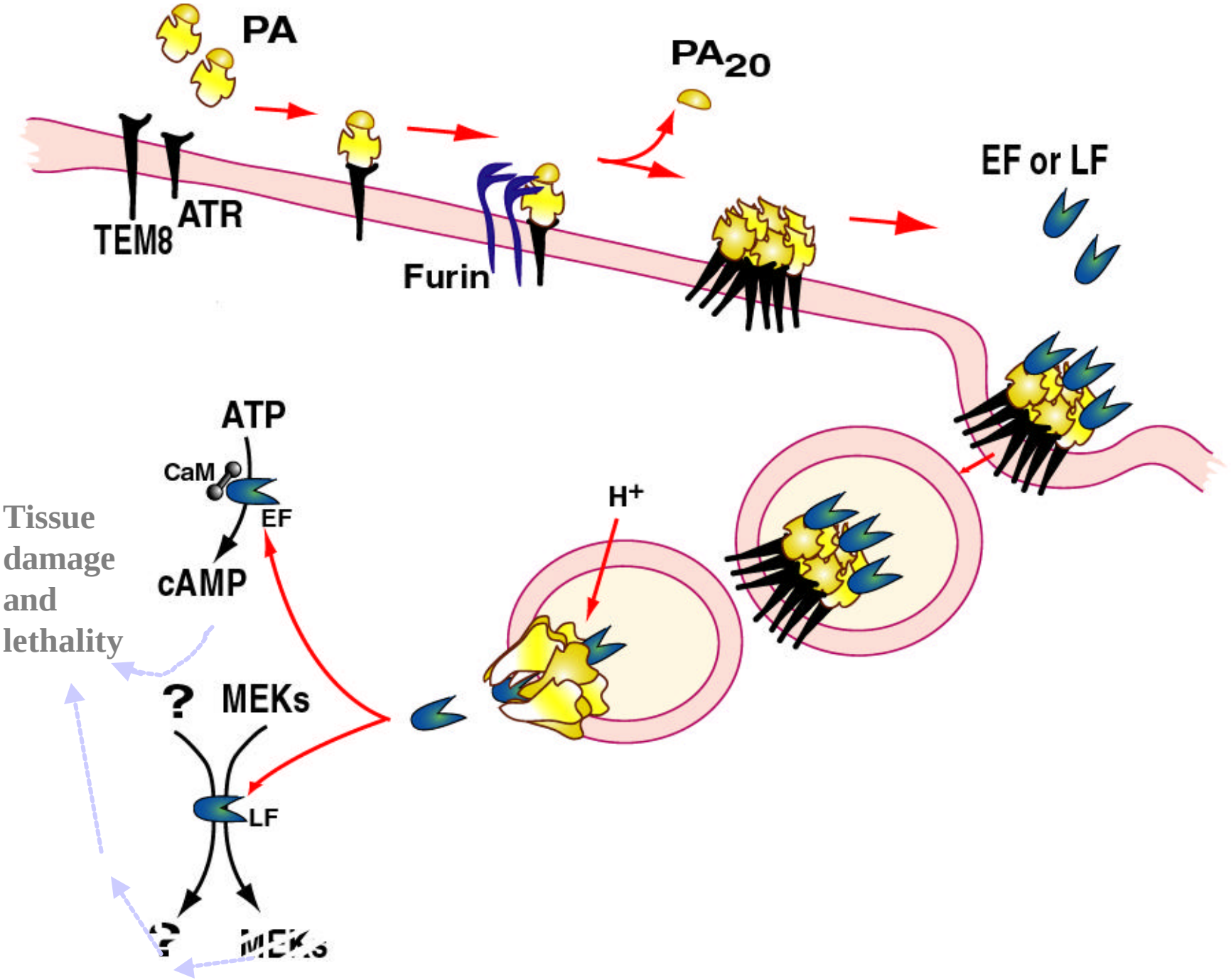
Infects domestic livestock, wild animals, humans

Two virulence factors encoded by separate large plasmids:

pXO2 γ-linked poly-D-glutamic acid capsule

pXO1 Three proteins combine to form two toxins, together constituting anthrax toxin:




PA
PA20
TEM8
ATR
Furin
EF or LF
ATP
CaM
EF
cAMP
H+
Tissue damage and lethality
? MEKs
LF

"Animal Rule" 21 CFR 601.91(a)(2-3)

- (2) The effect is demonstrated in more than one animal species with response expected to be **predictive for humans** OR a single animal model that is sufficiently well-characterized
- (3)The animal study endpoint is clearly **related to the desired benefit in humans**, generally survival enhancement or prevention of major morbidity

Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity Workshop, 4-23-2002

- In rhesus and rabbits, compared to humans
  - Relatively mild mediastinal involvement
  - Shorter time course of disease
  - Lower incidence of pneumonia
- Correlates of protection: Antibody to PA protects and correlates with immunity induced by AVA in rabbits and guinea pigs
- AVA or rPA vaccine-induced antibody or passively transferred anti PA antibody correlates with protection in rabbits (correlation is not absolute)
- Mouse model useful for assessing immunogenicity of PA; A/J mouse model used to develop potency assay for PA vaccine
- Nonhuman primate (NHP) is the model that best reproduces the human disease

Animal efficacy and relevance to humans

- Protection afforded by anti-PA antibody in multiples species is well documented
  - Little *et al*., Vaccine 22, 2004
- CDC AIG passive transfer
- Documented protection against aerosol challenge
  - **most likely route of exposure resulting from a bioterrorist event**
- Approval for protection against aerosol exposure will require data from aerosol challenge models using GLPs and validated elements/assays
  - Well-developed
  - Standardized
  - Reproducible
- Immune response to PA as measured by Toxin Neutralization Assay (TNA) and ELISA considered highly relevant
  - Quinn *et al*., JID 190, 2004

Anthrax Vaccines: Efficacy Testing and Surrogate Markers of Immunity Workshop, 4-23-2002 (cont.)

Recommendations were that:

- The whole immune response be investigated, not only the presence of antibody
- Passive and active immunizations be compared
- Comparison of kinetics (rate and level) of immune responses in animals versus humans
- Rabbit and NHP models be utilized

"Animal Rule" 21 CFR 601.91(a)(4)

- (4) The kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

NIAID Biodefense Research Web Site for rPA GUP and PEP

(http://www2.niaid.nih.gov/biodefense/research/products.htm)

- Developed in conjunction with representatives from CBER and DoD
- GUP only, not PEP, described below
- Human Immunogenicity
  - Early clinical trials to guide animal model development
  - Larger clinical trials later in development in conjunction with advanced animal model studies to better estimate protective efficacy in humans
- Animal Efficacy
  - Correlation of immune responses with protection
  - Active and passive protection studies
  - The vaccine dose and regimen given to the animals should generate a response equivalent to that achievable in humans.
  - challenge dose…..relevant to doses that would be expected in likely exposure scenarios for humans….also, a challenge with a dose expected to approximate a maximum human dose or determination of the maximum challenge dose at which the vaccine protects, should be considered.

Planned GUP Studies
(Rabbit and Rhesus)

- Correlates of Protection studies
  - Proof-of-concept efficacy (1 dose of vaccine in rabbits)
  - Dose ranging
  - Passive protection (human → rabbit and NHP)
- Duration of efficacy
- High-dose challenge
- Challenge with a non-Ames strain
- Pivotal/BLA enabling/Phase 3 studies
  - Bridging between early and late clinical product
  - Pivotal non-clinical efficacy studies
  - Pivotal passive transfer studies
  - Based on product-specific characteristics and data

Vaccine Development Challenges

- Clinical data needed to develop and refine animal models that “mimic” the human immune response
- Animal studies are not designed to show how well the vaccine performs in animals
- Animal studies are designed to delineate the minimum protective response
- Plasmapheresis incorporated into Phase 1 for initial passive transfer studies
- Variability of bioassays and immune assays require large numbers, probably not attainable for NHPs
- Model refinement requires validated system, well characterized challenge material, controlled dosing and well-characterized animals for challenge, to the extent possible

Vaccine Development Challenges (cont.)

- Availability of GLP facilities and expertise
- Availability of product for testing
- Long-term plan (timeline) to facilitate study design, resourcing and execution
- Tech transfer and validation of assays
- Production and qualification of assay reagents
- Agreement on key parameters of model such as challenge dose, challenge interval, etc.
- Agreement on major questions to be addressed, guides study sequence and design

Sources of Variability

- Challenge material source
  - Selection of challenge strain(s)
  - Standardization and characterization of challenge material
  - Harmonization of production, purification, characterization and use if multiple sites are involved
  - Robust potency/virulence test
- Apparatus/Equipment Controls
  - GLP documentation/QC control critical
  - Assays for assessing dose administration
  - Control exposure (i.e., respiratory rate monitoring, particle size)

(Provided courtesy of Dr. Lydia Falk, RAPS 2004)

Sources of Variability (cont.)

- In vivo activity of challenge material
  - Kinetics of distribution (e.g., spore kinetics and germination)
- Animal health and immunologic status
  - Need for quarantine
  - Pre-existing immunological status
  - Age
- Immunologic assay standardization
  - Standardized methodology
  - Assay and reference reagents
  - Validation

(Provided courtesy of Dr. Lydia Falk, RAPS 2004)

Importance of minimizing variability

- Advantages of reproducible animal model:
  - Allow use of fewer animals per experiment
  - Provide better predictability and increased efficiency in study design
  - Improved consistency among studies
  - Potentially decrease number of studies needed

The rPA Team

- Company PIs: Avecia-Matthew Duchars and VaxGen-Carmen Betancourt
- CBER: Drusilla Burns, Bruce Meade, Mark Abdy, Noreen Hynes
- DoD: Louise Pitt, Bruce Ivins
- CDC: Conrad Quinn, Nina Marano
- DHHS: Monique Mansoura, Carole Andres, Tom Fuerst
- CMB: Liz Osinski
- DMID
  - OBRA: Scott Winram, Eileen Flynn, Judy Hewitt, Ken Cremer, Helen Schiltz and Deborah Katz
  - ORA: Emily Kough, Carmen Maher, Beth Horigan and Lydia Falk
  - OCRA: Carol Ostrye, Steve Heyse and Holli Hamilton
  - OD: Carole Heilman, Pamela McInnes
  - GLP and assay consultants: Laureen Little and Sally Seaver
  - Contract Support
    - McKesson-Alicia Tatro; Regulatory and admin
    - EMMES Corp-Mark Wolff; Statistical analysis

The Battelle rPA Team

- Program Managers: Jim Estep, Bob Hunt
- Assay Project Manager: Kristin Long
- PEP Project Manager: Jason Mott
- Spore Preparation Project Team: Jennifer Browning, Jamie Austin, Ed Heller
- Spore Potency Project Manager: Dan Read
- Aerosol Model Refinement Project Manager: Roy Barnewall
- Study Directors: Pat Sabourin, Hank Lockman, Mark Perry, Michelle Clagett, Kathleen Marriott, Francey Reid, John Bigger
- Statisticians: Nancy Niemuth, Greg Stark